First application of fluorinated nitrones for the synthesis of fluoroalkylated -lactams via the Kinugasa reaction

Kowalski, Marcin K ; Mlostoń, Grzegorz ; Obijalska, Emilia ; Linden, Anthony ; Heimgartner, Heinz

Abstract: The regioselective reactions of fluorinated nitrones with selected terminal alkynes (Kinugasa reaction) was studied in the presence of Cu(I) iodide and TEA as a base. After chromatographic purification the desired -lactams were obtained in high yields (up to 93%) and high diastereoselectivities (up to 9:1). The reactions performed in the presence of chiral, enantiomerically pure ligands led to enantiomerically enriched products (ee values up to 26%) obtained as one of the possible diastereoisomers depending on the type of chiral ligand used.

DOI: https://doi.org/10.1016/j.tet.2016.06.073

First application of fluorinated nitrones for the synthesis of fluoroalkylated *β*-lactams via the Kinugasa reaction

Marcin K. Kowalski,[a] Grzegorz Mlostoń,[a,*] Emilia Obijalska,[a] Anthony Linden,[b] Heinz Heimgartner[b]

[a] Department of Organic and Applied Chemistry, Faculty of Chemistry, University of Łódź, Tamka 12, PL-91-403 Łódź (Poland)

[b] A. Linden, H. Heimgartner, Department of Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland

Dedicated to Professor Janusz Jurczak (Warsaw) on the occasion of his 75-th birthday

ABSTRACT

The regioselective reactions of fluorinated nitrones with selected terminal alkynes (Kinugasa reaction) was studied in the presence of Cu(I) iodide and TEA as a base. After chromatographic purification the desired *β*-lactams were obtained in high yields (up to 93%) and high diastereoselectivities (up to 9:1). The reactions performed in the presence of chiral, enantiomerically pure ligands led to enantiomerically enriched products (*ee* values up to 26%) obtained as one of the possible diastereoisomers depending on the type of chiral ligand used.

Keywords:
Fluorinated nitrones
[3+2]-cycloaddition
Kinugasa reaction
β-lactams
terminal acetylenes
copper (I) catalysis

*Corresponding author: Tel.: +48 42 635 57 61; Fax +48 42 665 54 24; e-mail address: gmloston@uni.lodz.pl

1. Introduction

In general, *β*-lactams are recognized as one of the most important classes of *N*-heterocycles with wide applications in medicine, biology and chemistry.[1] In addition, fluorinated organic compounds attract attention as important components of drugs, agrochemicals, polymers and materials with special properties.[2] Therefore, the development of methods for the synthesis of fluorinated *β*-lactams is a challenging task in modern organic synthesis.[3] Currently, several methods for their preparation are known, and some representative examples for the synthesis of trifluoromethyl-substituted *β*-lactams are presented in Fig. 1. The most important strategies are based on [2+2]-cycloadditions of fluorinated imines with differently substituted ketenes (Staudinger reaction),[4] ester enolate/imine cyclo-condensation,[5] and Reformatsky-type reactions.[6] Other important approaches are intramolecular *N*-acylation,[7] intramolecular *C*-alkylation,[8] and the ring expansion of 3-(trifluoromethyl)aziridine-2-carboxylates.[9]

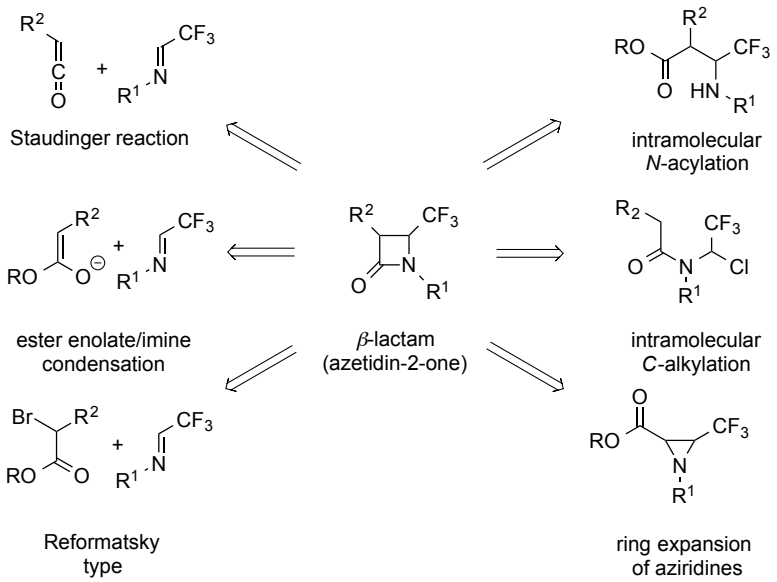
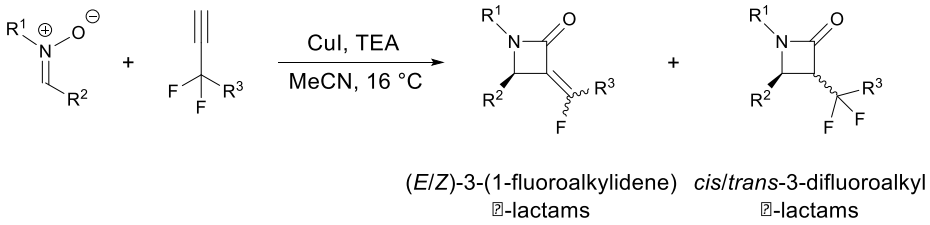


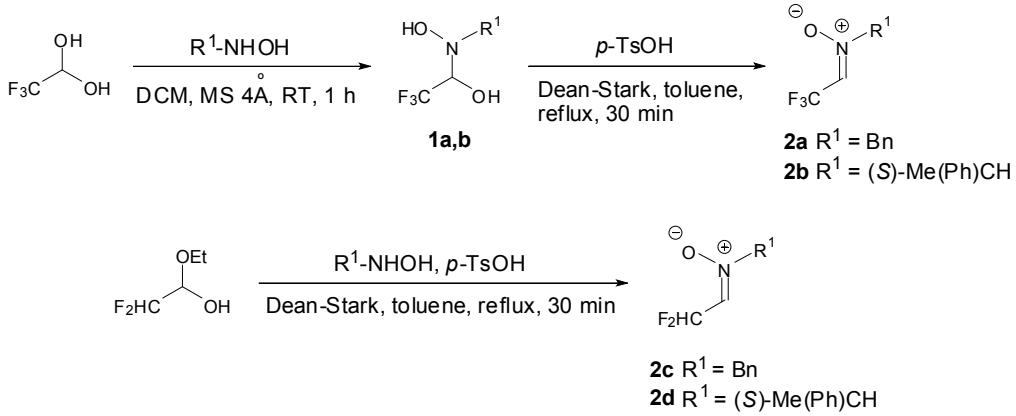
Figure 1. Some synthetic approaches to CF_3-substituted *β*-lactams.

The Kinugasa reaction[10] offers a general access to differently substituted *β*-lactams via the initial [3+2]-cycloaddition of the corresponding nitrones with terminal alkynes in the presence of a Cu(I) salt using a polar solvent (acetonitrile or formerly pyridine).[11] The initial [3+2]-cycloaddition occurs regioselectively, and the asymmetric version of the Kinugasa reaction has also been developed successfully.[12] Very recently, Grée and co-workers reported the results of their study on the Kinugasa reaction with propargylic *gem*-difluorides in which mixtures of 3-(difluoroalkyl) and/or 3-(1-fluoroalkylidene) *β*-lactams were obtained (Scheme 1).[13]



Scheme 1. Kinugasa reaction with fluorinated acetylenes leading to mixtures of fluorinated *β*-lactams.[13]

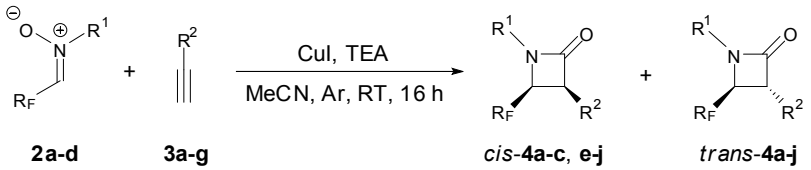
Due to our continuing interest in the development of methods for the preparation of fluorinated heterocycles, we present a new application of fluorinated nitrones for the preparation of fluroalkylated *β*-lactams via the Kinugasa reaction. In addition, the elaboration of an asymmetric version of the reaction was also of interest. For our studies, preparation of nitrones **2a**–**d**,[14a] derived from fluoral and difluoroacetaldehyde, was performed based on modified literature procedures (Scheme 2).[14b-d] Instead of a one-pot procedure a protocol with isolation of the intermediate hemiaminal of type **1** in the case of CF_3 derivatives was shown to be a more efficient one.



Scheme 2. Synthesis of fluorinated nitrones **2**.

2. Results and discussion

The isolated and purified nitrones **2a** and **2c** were used for the test reaction with phenylacetylene (**3a**) under the typical conditions for the Kinugasa reaction, i.e., using anhydrous MeCN, 0 ºC to room temperature, and CuI as a catalyst. Among several bases tested (TEA, dicyclohexylamine (Cy_2NH), Cy_2NMe, $CyNMe_2$, DABCO and DBU), TEA proved to be the most suitable one. In the case of **2a**, the crude reaction mixture was analyzed by ^{1}H NMR spectroscopy, which showed the presence of two isomeric *β*-lactams in a ratio of ca. 4:1 (*cis*-**4a**, *trans*-**4a**, Scheme 3). These diastereoisomers were separated by means of flash-column chromatography. The ^{1}H NMR spectrum of the major product (more polar fraction) showed a doublet at 4.64 ppm with $^3J(H,H)$ = 5.4 Hz attributed to *H*C(3) as well as a multiplet at 4.02–3.98 ppm for *H*C(4). The value of the coupling constant confirms the *cis* orientation of the H-atoms.[8,15] The corresponding coupling constant for the *trans* isomer was determined as $^3J_{H,H}$ = 2.4 Hz from the signal for *H*C(4), which appeared as a doublet × quartet at 3.85 ppm. Based on these data, the structures of the expected diastereomeric *β*-lactams *cis*- and *trans*-**4a** were confirmed (Scheme 3). In addition, the *cis*-configuration of the major product *cis*-**4a** was unambiguously established by X-ray crystallography (Fig. 2).



Scheme 3. Kinugasa reaction with fluorinated nitrones **2** and acetylenes **3** leading to fluorinated *β*-lactams **4**.

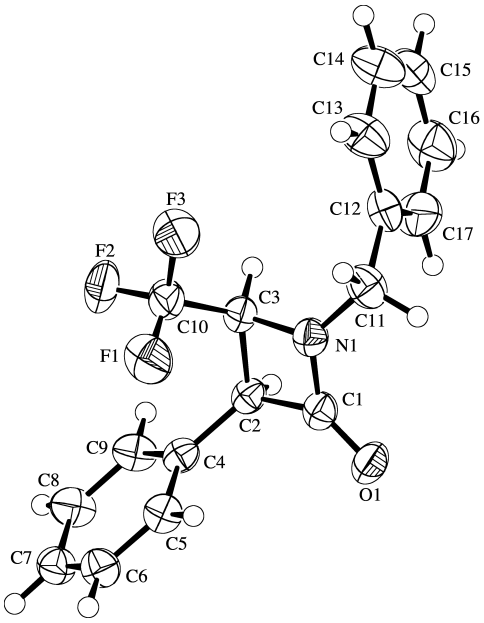
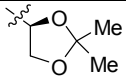


Figure 2. ORTEP[16] representation of the molecule *cis*-**4a** (arbitrary numbering of atoms, 50% probability ellipsoids; H-atoms given arbitrary displacement parameters).

Table 1.

Fluorinated *β*-lactams via Kinugasa reaction.

Nitrone	R_F	R^1	Acetylene	R^2	*β*-Lactam	Total yield[a])	*cis*/*trans*	Reaction time [h]
2a	CF_3	Bn	**3a**	Ph	**4a**	89	83/17[c])	16
2a	CF_3	Bn	**3b**	$CH(OEt)_2$	**4b**	68	71/29[c])	16
2a	CF_3	Bn	**3c**	4-F-C_6H_4	**4c**	90	30/70[c])	36

2a	CF_3	Bn	**3d**	CO_2Me	**4d**	51[b])	0/100[c])	36
2a	CF_3	Bn	**3e**	*t*-Bu	**4e**	59	24/76[c])	16
2a	CF_3	Bn	**3f**	Ferrocenyl	**4f**	70[b])	10/90[d])	16
2a	CF_3	Bn	**3g**		**4g**	82	41/50/9[d])[e])	36
2b	CF_3	(*S*)-Me(Ph)CH	**3a**	Ph	**4h**	61	14/11/24/51[d])	16
2c	CHF_2	Bn	**3a**	Ph	**4i**	93	70/30[d])	16
2d	CHF_2	(*S*)-Me(Ph)CH	**3a**	Ph	**4j**	58	9/18/73[d])	16

[a]) Total yield of pure mixture of diastereoisomers

[b]) Isolated *trans*-isomer

[c]) Calculated based on the amount of isolated pure isomers

[d]) Determined by ^{1}H NMR spectroscopy in the isolated pure mixture of diastereoisomers

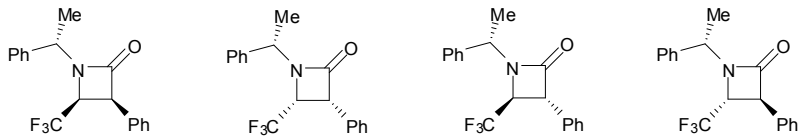
[e]) Only one isomer was isolated as a pure fraction (less polar) (see Experimental)

The reaction of **2c** and **3a** under the same conditions also yielded a mixture of diastereoisomeric *β*-lactams, *cis*- and *trans*-**4i** (ca. 7:3), in 93% yield. However, in this case, attempted chromatographic separation of the isomers was unsuccessful.

The analogous protocol was applied to reactions of **2a** with acetylenes **3b**-**g**, and in all cases, except with **3d** (R = CO_2Me), mixtures of the expected *cis*- and *trans*-*β*-lactams were obtained diastereoselectively. While in the case of **3b** the major isomer was also identified as the *cis*-diastereoisomer, the *trans*-isomer was found to be the predominant product of the reactions performed with ethynylferrocene (**3f**) as well as with 4-fluorophenyl- (**3c**), *tert*-butyl- (**3e**), and (*R*)-2,2-dimethyl-1,3-dioxolan-4-yl- (**3g**) substituted acetylene. Furthermore, the reaction with methyl propiolate (**3d**) led to the *trans*-disubstituted *β*-lactam, *trans*-**4d**, exclusively. In the latter case, the diagnostic coupling constant $^3J(H\text{C}(3),H\text{C}(4))$ was 2.1 Hz.

While the *cis*- and *trans*-isomers of **4a**–**f** and **4i** were obtained as racemic materials, the products of the reaction of **2a** with enantiopure **3g** were optically active, formed in a diastereoselective manner. Thus, chromatographic workup of **4g** led to two fractions. The less polar fraction consists of a pure diastereoisomer, but the more polar fraction was identified as a mixture of two other diastereoisomers. Based on the amounts of isolated fractions and the registered ^{1}H and ^{19}F NMR spectra, the ratio of these products was calculated to be 41/50/9 (Table 1). In analogy to **4a**-**e**, the product in the less polar fraction was assigned as the *trans*-configured isomer ((*S*)-*trans*-**4g**) and two other products, obtained in the more polar fraction, are postulated to display the *cis*-configuration within the *β*-lactam ring ((*S*)-*cis*-**4g'** and (*S*)-*cis*-**4g''**).

Similarly, the reaction of nitrone **2b** containing the (*S*)-methylbenzyl substituent as R^1 with phenylacetylene (**3a**) under standard conditions led to a mixture of four optically active diastereoisomeric *β*-lactams (Figure 3) in a ratio of 14/11/24/51 (Table 1). After chromatographic workup, three of these products were isolated as pure isomers. Two of them were identified as *trans* isomers ((*S*)-*trans*-**4h** (16%) and (*S*)-*trans*-**4h'** (38%)) on the basis of the *H*C(3),*H*C(4) coupling constant ($^{3}J(H,H)$) of 2.4 Hz in both cases. The corresponding coupling constant of the third product, isolated in 7% yield, was determined to be $^{3}J(H,H)$ = 6.0 Hz, indicating the *cis*-configuration ((*S*)-*cis*-**4h''**).



(*S*)-*cis*-**4h** (*S*)-*cis*-**4h'** (*S*)-*trans*-**4h** (*S*)-*trans*-**4h'**

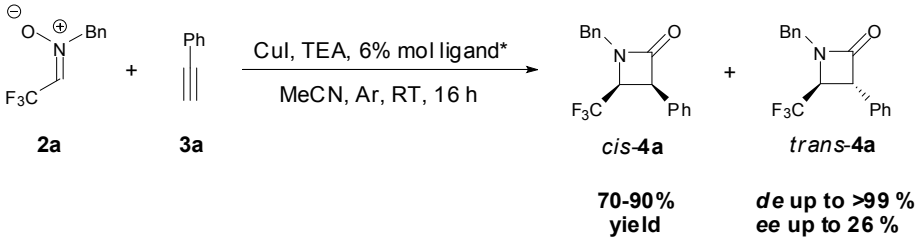
Figure 3. Diastereoisomeric *β*-lactams from the reaction of **2b** with **3a**.

Finally, the chiral nitrone **2d** reacted with **3a** to give a mixture of three stereoisomeric *β*-lactams **4j** (in ratio of 9/18/73) in 58% yield. In this case, attempted separation of the isomers was unsuccessful.

The stepwise mechanism of the Kinugasa reaction has been proposed by many authors.[11e,f] The initial regioselective [3+2]-cycloaddition of the nitrone onto the C≡C bond is postulated to be followed by the ring contraction of the isoxazoline to give the four-membered azetidin-2-one ring. It seems likely that the cis-*β*-lactams **4a-**

d,**g**,**i** are formed as kinetically controlled products and in the case of **4c**,**d**, containing an activated, acidic HC(3) moiety, undergoes fast isomerization to the thermodynamically more stable *trans*-products. On the other hand, in the case of derivatives bearing a bulky substituent at C(3)- or at the N-atom (i.e. in compounds **4e**,**f**,**h**,**j**), steric hindrance can govern the cycloaddition step in favour of the sterically less congested *trans*-*β*-lactams.

The asymmetric Kinugasa reaction has been studied extensively, and ligands containing the bis-oxazoline motif as well as BINOL were applied successfully.[11e,12,17] In the present study, three bis-oxazoline ligands **L1**-**L3** (Figure 4) were applied to induce the asymmetric course of the reaction of **2a** with phenylacetylene (**3a**). In addition, two other ligands **L4** and **L5** were also tested. In experiments performed in the presence of **L1**-**L4**, the formation of only one diastereoisomer with complete diastereoselectivity was observed. However, while with **L2**, **L3**, and **L4** diastereoselective formation of *trans*-*β*-lactams was observed, the reaction performed in the presence of **L1** gave the *cis*-configured product **4a** exclusively. In contrast, reaction of **2a** with **3a** carried out in the presence of ligand **L5** afforded a mixture of *cis*-**4a** and *trans*-**4a** in a ratio of 60/40 (Scheme 4). In the latter case, after preliminary purification, the ratio of the diastereoisomers *cis*/*trans*-**4a** was determined by ^{1}H NMR spectroscopy. The *ee* values for the diastereoisomers were obtained from the HPLC analysis using a Phenomenex Lux Cellulose-1 chiral column. The determined *ee* values of the obtained products were generally low and in the best case, i.e. product *trans*-**4a**, obtained in the experiment with **L4** as a ligand, was determined to be 26%. In order to check the reported, high enantioselectivities in the Kinugasa reaction with *C*-phenyl nitrones in the presence of the ligand **L2**,[17a] the reaction of *C,N*-diphenyl nitrone with **3a** was repeated in our laboratory and the obtained results were consistent with the reported data (high diasteroselectivity (dr = 93:7) and enantioselectivity (94%) for the major *cis*-isomer). For that reason, we postulate tentatively that the low enantioselectivity observed in the reaction with nitrone **2a** may result from the presence of the CF_3 group (instead of the Ph substituent), which does not coordinate efficiently enough with another Ph-ring of **3a** as it was postulated in the stereochemical model of the Kinugasa reaction presented in literature for the *C,N*-diphenyl nitrone.[11e,17b]



Scheme 4. Asymmetric Kinugasa reaction of the fluorinated nitrone **2a** with phenylacetylene (**3a**).

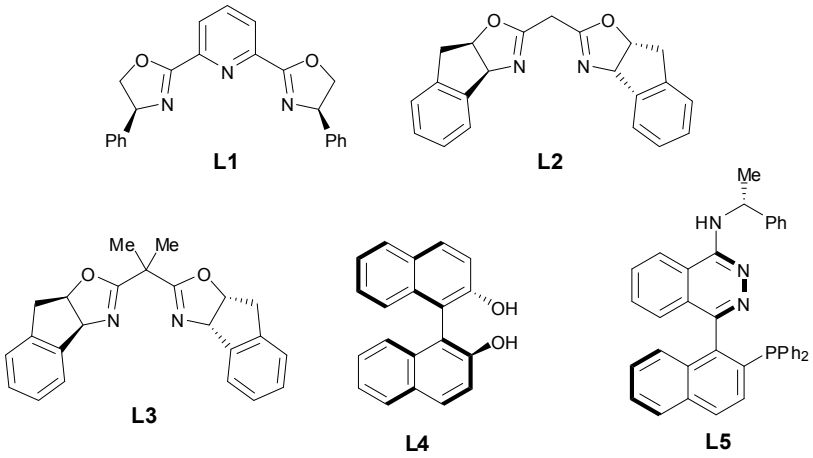


Figure 4. Chiral ligands applied in the asymmetric Kinugasa reaction.

3. Conclusions

As there is growing interest in the synthesis of fluorinated *β*-lactams and their applications,[18] a need for the elaboration of new methods for their synthesis is emerging and their development is a challenging task for the modern organic synthesis. The novel Kinugasa approach based on the application of relatively little known fluorinated nitrones is presented for the first time. Different mono-substituted acetylenes were shown to react with fluorinated nitrones under typical Kinugasa reaction conditions, and the expected 4-trifluoromethyl- and 4-difluoromethyl-*β*-lactams were formed in good to high yields. The *cis*/*trans*-diastereoselectivity varied depending on the type of substituent on the acetylene used in the reaction. In the case of a chiral, enantiopure nitrone, mixtures of optically active diastereoisomers were formed. The attempted asymmetric Kinugasa reaction with phenylacetylene and

the achiral *N*-benzyl *C*-trifluoromethyl nitrone in the presence of a catalytic amount of different chiral ligands led to a remarkable increase in the diastereoselectivity, although the observed *ee*-values were low.

The presented approach supplements a very recently reported protocol, in which fluorinated acetylenes were reacted with nitrones.[13] However, in that case, mixtures of 3-fluoroalkylidene- and 3-difluoroalkyl-*β*-lactams were obtained. Thus, the *β*-lactams described in the present study differ from those reported.[13] by the fact that the fluorinated alkyl group is located at C(4) exclusively.

4. Experimental section

4.1. General

Melting points were determined on a Stuart SMP30 apparatus in capillaries. The ^{1}H, $^{13}C\{^{1}H\}$, and ^{19}F NMR spectra were recorded on a Bruker Avance III (600, 150 and 565 MHz, respectively), or in the case of $^{19}F\{^{1}H\}$ on a Bruker Avance III 200 (188 MHz) spectrometer using the solvent signal as reference; chemical shifts (δ) in ppm and coupling constants J in Hz. Assignments of signals in ^{13}C NMR spectra were achieved using HMQC and HMBC techniques. IR spectra were measured using a NEXUS FT-IR spectrophotometer. The ESI-HRMS spectra were recorded using a Waters GCT Premier High Resolution mass spectrometer or on a Bruker MAXIS spectrometer. Specific rotations ($[\alpha]_D^{22}$) were measured on a PERKIN-ELMER 241 MC polarimeter for λ = 589 nm, in dichloromethane at room temperature and their values are given in 10^{-1} deg cm^2 g^{-1}.

All solvents were used as commercial products. Trifluoroacetaldehyde hydrate (75%) and difluoroacetaldehyde ethyl hemiacetal (95%) were purchased from FluoroChem. Anhydrous acetonitrile was purchased from Acros and was degassed before use. Nonchiral and chiral enantiomerically pure *N*-hydroxylamines were prepared according to the known literature protocols.[19]

4.2. Synthesis of nitrones derived from fluoral and difluoroacetaldehyde.

***N*-Benzyl-*N*-(2,2,2-trifluoro-1-hydroxyethyl)hydroxylamine (*N*-Benzyl *C*-(trifluoromethyl)nitrone hydrate; 1a)**, ***N*-Benzyl *C*-(trifluoromethyl)nitrone (2a),**

and ***N*-Benzyl *C*-(difluoromethyl)nitrone (2c)** were prepared following the published protocol.[14a]

***N*-(*S*)-Methylbenzyl-*N*-(2,2,2-trifluoro-1-hydroxyethyl)hydroxylamine (*N*-(*S*)-Methylbenzyl-*C*-(trifluoromethyl)nitrone hydrate; 1b).**

Trifluoroacetaldehyde hydrate (75%) (1.08 g, 6.5 mmol) was added to a solution of freshly prepared *N*-(*S*)-(methylbenzyl)hydroxylamine (685 mg, 5.0 mmol) in dichloromethane (10 ml). The reaction was carried out at room temperature in the presence of activated molecular sieves 4 Å for 1 h. Then, an additional portion of drying agent (Na_2SO_4) was added. After filtration, the solvent was evaporated and crude hemiaminal was obtained in nearly quantitative yield (1.07 g) as a colorless liquid, and was used for the next step without purification.

***N*-(*S*)-Methylbenzyl *C*-(trifluoromethyl)nitrone (2b)**.[14d]

The crude hemiaminal described above was suspended in toluene (15 ml) and a catalytic amount of *p*-TsOH·H_2O (19 mg, 0.1 mmol) was added. The mixture was heated at reflux in a Dean-Stark apparatus. After ca. 30 min, the water had been removed completely and the solvent was evaporated *in vacuo*. Pure product was obtained after purification by flash column chromatography (conditions: Grace Reveleris X2 apparatus with UV-Vis and ELSD detection, using commercially available SiO_2 columns 12 g or 24 g, pressure 20 psi, solvent flow rate 25 ml/min) using petroleum ether with increasing amounts of ethyl acetate (up to 8:2) as eluent.

Colorless solid nitrone **2b** (879 mg, 81% yield, purification on SiO_2, using petroleum ether/AcOEt = 90:10)); m.p. 111–113 ºC (petroleum ether/Et_2O); $[\alpha]_D^{22}$ = –20.0 (c 1.0 in DCM); IR (KBr): ν_{max}/cm^{-1} 3096s, 3026w, 1591vs (HC=N), 1457s, 1247s, 1204vs, 1152vs, 913s, 703s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.48–7.43 (m, 5 CH_{Ar}), 6.97 (q, $^3J(H,F)$ = 6.0 Hz, 1H, F_3CC*H*=N), 5.16 (q, $^3J(H,H)$ = 7.2 Hz, 1H, CH_3(C*H*)Ph), 1.87 (d, $^3J(H,H)$ = 6.6 Hz, 3H, CH_3(CH)Ph); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 136.7 (1 C_{Ar}), 129.5, 129.1, 127.3 (5 CH_{Ar}), 122.2 (q, $^2J(C,F)$ = 41.1 Hz, F_3C*C*H=N); 119.6 (q, $^1J(C,F)$ = 268.2 Hz, CF_3), 76.4 (CH_3(*C*H)Ph)), 18.4 (CH_3(CH)Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –65.94 (d, $^3J(F,H)$ = 5.1 Hz, 3F, CF_3); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{10}H_{10}F_3NONa$, 240.0606, found 240.0607.

***N*-(*S*)-Methylbenzyl *C*-(difluoromethyl)nitrone (2d).**

Difluoroacetaldehyde ethyl hemiacetal (95%) (897 mg, 6.5 mmol) was added to a solution of freshly prepared enantiomerically pure *N*-(*S*)-(methylbenzyl)hydroxylamine (685 mg, 5.0 mmol) and a catalytic amount of *p*-TsOH·H_2O (19 mg, 0.1 mmol) in toluene (10 ml). The mixture was heated at reflux in a Dean-Stark apparatus until evolution of water was finished (ca. 30 min), and then the solvent was evaporated under reduced pressure. Analytically pure product was obtained after purification by flash column chromatography (conditions: Grace Reveleris X2 apparatus with UV-Vis and ELSD detection, using commercially available SiO_2 columns, 12 g or 24 g, pressure 20 psi, solvent flow rate 25 ml/min) using petroleum ether with increasing amounts of ethyl acetate (up to 8:2) as eluent.

Colorless solid nitrone **2d** (796 mg, 80% yield, purification on SiO_2, using petroleum ether/AcOEt = 90:10); m.p. 67–70 ºC (petroleum ether/Et_2O); $[\alpha]_D^{22}$ = –60.6 (c 1.0 in DCM); IR (KBr): ν_{max}/cm^{-1} 3166w, 3089s, 3033w, 1589vs (C=N), 1462s, 1290s, 1112vs, 1049vs, 696vs; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.48–7.46 (m, 2 CH_{Ar}), 7.43–7.40 (m, 3 CH_{Ar}), 7.09–7.03 (m, 1H, (F_2HC*C*H=N)), 6.68 (dt, ^{2}*J(H,F)* = 53.4 Hz, ^{3}*J(H,H)* = 5.3 Hz, 1H, (F_2*H*CCH=N), 5.11 (q, ^{3}*J(H,H)* = 6.9 Hz, 1H, CH_3(C*H*)Ph), 1.83 (d, ^{2}*J(H,H)* = 7.0 Hz, 3H, C*H*$_3$(CH)Ph); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 137.0 (1 *C*$_{Ar}$), 128.3 (t, ^{2}*J(C,F)* = 32.6 Hz, F_2HC*C*H=N), 129.3, 129.0, 127.4 (5 *C*H$_{Ar}$), 108.9 (t, ^{1}*J(C,F)* = 231.0 Hz, F_2H*C*CH=N), 75.1 (CH_3(*C*H)Ph), 18.8 (*C*H_3(CH)Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –121.46, –121.34 (2s, 2F, CH*F*$_2$); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{10}H_{11}F_2NONa$, 222.0706, found 222.0704.

4.3. General Procedure for the Preparation of *β*-Lactams 4 (Kinugasa Reaction).

To an oven-dried flask, equipped with a septum, stirring bar and a balloon filled with argon was added CuI (190 mg, 1.0 mmol). Then, anhydrous and degassed acetonitrile (2 ml) was added. To the stirred suspension (ice bath), a mixture of the appropriate acetylene **3** (1.0 mmol) was added. After 5 min, a solution of dry triethylamine (TEA, 202 mg, 2.0 mmol) in anhydrous and degassed MeCN (3 ml) was added at 0 °C (ice bath) while stirring under an inert atmosphere, and after 10 min, a solution of a fluorinated nitrone **2** (2.0 mmol) in dry acetonitrile

(3 ml) was added. After another 10 min, the ice bath was removed and the reaction mixture was left at room temperature for 16 or 36 h. Then, dichloromethane (DCM, 5 ml) was added and the solvents were removed under reduced pressure. Crude products were purified by flash column chromatography (conditions: Grace Reveleris X2 apparatus with UV-Vis and ELSD detection, using commercially available 12 g or 24 g SiO_2 columns, pressure 20 psi, solvent flow rate 25 ml/min) using petroleum ether with increasing amounts of ethyl acetate (up to 7:3) as eluent.

For the asymmetric version of the reaction, the appropriate chiral ligand **L1-5** (0.06 mmol) dissolved in dry acetonitrile (1 ml) was added to the stirred suspension of CuI (190 mg, 1.0 mmol) in anhydrous and degassed acetonitrile (2 ml), and the mixture was stirred at room temperature for 2 h. The solution was cooled to 0 °C and a solution of TEA (2.0 mmol) in dry MeCN was added. After 10 min, a solution of phenylacetylene (**3a**) was added, followed by nitrone **2a** dissolved in anhydrous MeCN after 30 min. The ice bath was removed after 15 min, and the reaction mixture was left at room temperature for 16 h under inert atmosphere. Workup was carried out as described above. The diastereoselectivity was determined by analysis of the ^{1}H NMR spectra obtained from the preliminarily purified product. Enantiomeric excess was determined using chiral HPLC with a Phenomenex Lux Cellulose-1 column.

***trans*-*N*-Benzyl-3-phenyl-2-(trifluoromethyl)azetidin-2-one (*trans*-4a).**

Orange oily *β*-lactam ***trans*-4a** (45 mg, 15% yield, purification on SiO_2, using petroleum ether/AcOEt = 95:5, less polar fraction); IR (film): ν_{max}/cm^{-1} 3091w, 3057w, 3032w, 2931w, 1776vs (C=O), 1498s, 1453s, 1396s, 1281s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.43–7.33 (m, 8 C*H*$_{Ar}$), 7.26–7.25 (m, 2 C*H*$_{Ar}$), 5.01, 4.10 (AB system, ^{2}*J(H,H)* = 15.0 Hz, 2H, C*H*$_2$Ph), 4.50 (brs, 1H, C(3)*H*), 3.85 (dq, ^{3}*J(H,H)* = 2.4 Hz, ^{3}*J(H,F)* = 6.4 Hz, 1H, C(4)*H*); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 166.5 (*C*=O), 134.7, 132.7 (2 *C*$_{Ar}$), 129.2, 129.1, 128.6, 128.3, 128.2, 127.3 (10 *C*H$_{Ar}$), 124.4 (q, ^{1}*J(C,F)* = 278.3 Hz, *C*F$_3$), 58.0 (q, ^{2}*J(C,F)* = 33.8 Hz, *C*(4)H), 56.4 (*C*(3)H), 45.8 (*C*H$_2$Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –73.69 (d, 3F, ^{3}*J(H,F)* = 6.4 Hz, C*F*$_3$); HRMS/ESI *(m/z)* [M+Na]$^+$ calcd for $C_{17}H_{14}F_3NONa$, 328.0919, found 328.0925; Racemic mixture: HPLC (Phenomenex Lux Cellulose-1 column, hexane/*i*-PrOH = 9:1, flow rate = 0.6

ml/min, λ = 210 nm, t_R = 7.70 min (first enantiomer), t_R = 8.73 min (second enantiomer).

***cis*-*N*-Benzyl-3-phenyl-2-(trifluoromethyl)azetidin-2-one (*cis*-4a).**

Colorless semi-solid *β*-lactam ***cis*-4a** (226 mg, 74% yield, purification on SiO_2, using petroleum ether/AcOEt = 90:10, more polar fraction); m.p. 102–103 ºC; IR (KBr): v_{max}/cm^{-1} 3032 w, 2928w, 2854w, 1751vs (C=O), 1449w, 1371w, 1285s, 1130vs, 698s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.32–7.21 (m, 10 *C*H(arom.)), 4.64 (d, $^3J(H,H)$ = 5.4 Hz, 1H, C(3)*H*), 4.02–3.98 (m, 1H, C(4)*H*), 3.97, 4.91 (AB system, 2d, $^2J(H,H)$= 15.0 Hz, 2H, CH_2Ph); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 166.8 (*C*=O), 134.6, 130.2 (2 C_{Ar}), 129.1 (brs, 2 CH_{Ar}), 129.0, 128.6, 128.5, 128.3 (8 CH_{Ar}), 123.8 (q, $^1J(C,F)$ = 278.9 Hz, CF_3), 57.0 (*C*(3)H), 55.7 (q, $^2J(C,F)$ = 31.5 Hz, *C*(4)H), 45.7 (*C*H_2Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –68.80 (d, 3F, ^{3}J(*H,F)* = 6.2 Hz, CF_3); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{17}H_{14}F_3NONa$, 328.0919, found 328.0925; Racemic mixture: HPLC (Phenomenex Lux Cellulose-1 column, hexane/i-PrOH = 9:1, flow rate = 0.6 ml/min, λ = 210 nm, t_R = 5.24 min (first enantiomer), t_R = 5.91 min (second enantiomer).

***trans*-*N*-Benzyl-3-(diethoxymethyl)-2-(trifluoromethyl)azetidin-2-one (*trans*-4b).**

Pale yellow oily *β*-lactam ***trans*-4b** (65 mg, 20% yield, purification on SiO_2, using petroleum ether/AcOEt = 95:5, less polar fraction); IR (KBr): v_{max}/cm^{-1} 3035w, 2961s, 2979s, 2929m, 2979m, 1779vs (C=O), 1401s, 1279vs, 1193vs, 1132vs, 1055vs, 692s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.39–7.32 (m, 5 CH_{Ar}), 4.82 (d, $^3J(H,H)$ = 2.4 Hz 1H, C*H*$(OEt)_2$), 4.05 (dq, $^3J(H,H)$ = 1.8 Hz, $^3J(H,F)$ = 5.4 Hz, 1H, C(4)*H*), 4.95, 3.96 (AB system, 2d, $^2J(H,H)$ = 15.6 Hz, 2H, CH_2Ph), 3.57–3.55 (m, 1H, C(3)*H*), 3.82–3.80, 3.68–3.58, 3.53–3.48 (3m, 4H, 2 CH_3CH_2O), 1.22–1.19 (m, 6H, 2 CH_3CH_2O); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 165.1 (*C*=O), 134.4 (1 C_{Ar}), 128.7, 128.4 127.9 (5 CH_{Ar}), 124.5 (q, $^1J(C,F)$ = 277.7 Hz, CF_3), 98.4 (*C*$H(OEt)_2$), 64.2, 63.3 (2 CH_3CH_2O), 55.9 (*C*(3)H), 51.2 (q, $^2J(C,F)$ = 34.3 Hz, *C*(4)H), 45.4 (*C*H_2Ph), 15.0, 15.1 (2 CH_3CH_2O); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –73.74 (d, 3F, $^3J(H,F)$ = 6.2 Hz, CF_3); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{16}H_{20}F_3NO_3Na$, 354.1293, found 354.1293.

***cis*-*N*-Benzyl-3-(diethoxymethyl)-2-(trifluoromethyl)azetidin-2-one (*cis*-4b).**

Yellow oily *β*-lactam ***cis*-4b** (160 mg, 48% yield, purification on SiO_2, using petroleum ether/AcOEt = 90:10, more polar fraction); IR (KBr): ν_{max}/cm^{-1} 3033w, 2976vs, 2935s, 2929w, 2979w, 1779vs (C=O), 1462s, 1387s, 1293vs, 1173vs, 1107vs, 1053vs, 689s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.39–7.32 (m, 3 C*H*$_{Ar}$), 7.27–7.26 (m, 2 C*H*$_{Ar}$), 4.93 (d, ^{3}*J(H,H)* = 8.2 Hz, 1H, C*H*(OEt)$_2$), 4.88, 4.02 (AB system, 2d, ^{2}*J(H,H)* = 15.1 Hz, 2H, C*H*$_2$Ph), 3.90–3.86 (m, 1H, C(4)*H*), 3.80–3.70 (m, 4H, 2 CH_3CH_2O), 3.53–3.48 (m, 1H, C(3)*H*), 1.29, 1.19 (2t, ^{3}*J(H,H)* = 7.0 Hz, 6H, 2 C*H*$_3$CH$_2$O); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 165.2 (*C*=O), 134.6 (1 *C*$_{Ar}$), 129.0, 128.4, 128.2 (5 *C*H$_{Ar}$), 124.4 (q, ^{1}*J(C,F)* = 277.5 Hz, *C*F$_3$), 97.9 (brd, ^{4}*J(C,F)* = 1.4 Hz, *C*H(OEt)$_2$), 62.8, 62.2 (2 CH_3CH_2O), 56.4 (*C*(3)H), 52.8 (q, ^{2}*J(C,F)* = 33.9 Hz, *C*(4)H), 45.6 (*C*H$_2$Ph), 15.2, 14.8 (2 *C*H$_3$CH$_2$O); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –68.80 (d, 3F, ^{3}*J(H,F)* = 6.0 Hz, C*F*$_3$). HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{16}H_{20}F_3NO_3Na$, 354.1293, found 354.1295.

***trans*-*N*-Benzyl-3-(4-fluorophenyl)-2-(trifluoromethyl)azetidin-2-one (*trans*-4c).**
Pale yellow solid *β*-lactam ***trans*-4c** (204 mg, 63% yield, purification on SiO_2, using petroleum ether/AcOEt = 95:5, less polar fraction); m.p. 46–48 ºC; IR (KBr): ν_{max}/cm^{-1} 3073w, 3029w, 2927w, 2891s, 1766vs (C=O), 1502vs, 1401s, 1313s, 1288s, 1225s, 1184vs, 1148vs, 1123vs, 950s, 825s, 731s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.42–7.33 (m, 5 C*H*$_{Ar}$), 7.23–7.20 (m, 2 C*H*$_{Ar}$), 7.08–7.04 (m, 2 C*H*$_{Ar}$), 4.47 (brd, ^{3}*J(H,H)* = 2.4 Hz, 1H, C(3)*H*), 4.99, 4.08 (AB system, 2d, ^{2}*J(H,H)* = 15.0 Hz, 2H, C*H*$_2$Ph), 3.78 (dq, ^{3}*J(H,H)* = 2.4 Hz, ^{3}*J(H,F)* = 5.8 Hz, 1H, C(4)*H*); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 166.2 (*C*=O), 162.5 (d, ^{1}*J(C,F)* = 246.0 Hz, F*C*$_{Ar}$), 134.6 (1 *C*$_{Ar}$), 129.1, 129.0, 128.9, 128.5, 128.3 (7 *C*H$_{Ar}$), 124.2 (q, ^{1}*J(C,F)* = 278.3 Hz, *C*F$_3$), 116.1 (d, ^{2}*J(C,F)* = 21.6 Hz, 2 CH$_{Ar}$), 58.0 (q, ^{2}*J(C,F)* = 33.8 Hz, *C*(4)H), 55.6 (*C*(3)H), 48.8 (*C*H$_2$Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –73.74 (d, ^{3}*J(H,F)* = 5.8 Hz, 3F, C*F*$_3$), –(113.29–113.34) (m, 1F, *F*C$_{Ar}$); HRMS/ESI *(m/z)* $[M+H]^+$ calcd for $C_{17}H_{14}F_4NO$, 324.1006, found 324.1007.

***cis*-*N*-Benzyl-3-(4-fluorophenyl)-2-(trifluoromethyl)azetidin-2-one (*cis*-4c).**
Pale yellow solid *β*-lactam ***cis*-4c** (87 mg, 27% yield, purification on SiO_2, using petroleum ether/AcOEt = 90:10, more polar fraction); m.p. 60–63 ºC; IR (KBr): ν_{max}/cm^{-1} 3032w, 2934w, 2891s, 1758vs (C=O), 1515s, 1299s, 1159s, 1128s, 819s, 692s, 532w; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.43–7.29 (m, 7 C*H*$_{Ar}$), 7.08–7.04 (m, 2 C*H*$_{Ar}$), 5.01 (d, ^{2}*J(H,H)* = 15.0 Hz, 1H of AB system from C*H*$_2$Ph), 4.73 (d, ^{3}*J(H,H)* = 6.0 Hz, 1H, C(3)*H*), 4.12–4.07 (m, 2H, C(4)*H*, 1H of AB system from C*H*$_2$Ph); ^{13}C

NMR (150 MHz, $CDCl_3$), *δ*: 166.6 (*C*=O), 162.6 (d, $^1J(C,F)$ = 246.0 Hz, FC_{Ar}), 134.4 (1 C_{Ar}), 130.9 (d, $^3J(C,F)$ = 8.1 Hz, 2 CH_{Ar}), 129.1, 128.6, 128.3 (5 CH_{Ar}), 126.0 (d, $^4J(C,F)$ = 3.3 Hz, 1 C_{Ar}), 123.8 (q, $^1J(C,F)$ = 278.7 Hz, CF_3), 115.6 (d, $^2J(C,F)$ = 21.5 Hz, 2 CH_{Ar}), 56.2 (*C*(3)H), 55.6 (q, $^2J(C,F)$ = 31.7 Hz, *C*(4)H), 45.7 (CH_2Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –68.30 (d, $^3J(H,F)$ = 6.2 Hz, 3F, CF_3), –(113.27–113.33) (m, 1F, FC_{Ar}); HRMS/ESI *(m/z)* $[M+H]^+$ calcd for $C_{17}H_{14}F_4NO$, 324.1006, found 324.1006.

***trans*-*N*-Benzyl-3-methoxycarbonyl-2-(trifluoromethyl)azetidin-2-one (*trans*-4d).** Colorless oily *β*-lactam ***trans*-4d** (147 mg, 51% yield, purification on SiO_2, using petroleum ether/AcOEt = 92:8); IR (film): ν_{max}/cm^{-1} 3052w, 3030w, 3032w, 2942w, 2921w, 1770vs (C=O), 730s (C=O), 1480s), 1440s, 1397w, 1271s, 1195s, 729s, 701s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.32–7.27 (m, 2 CH_{Ar}), 7.27–7.25 (m, 1 CH_{Ar}), 7.20–7.18 (m, 2 CH_{Ar}), 4.12 (dq, $^3J(H,H)$ = 2.1 Hz, $^3J(H,F)$ = 6.1 Hz, 1H, C(4)*H*), 4.03 (d, $^3J(H,H)$ = 2.1 Hz, 1H, C(3)*H*), 4.80, 3.98 (AB system, 2d, $^2J(H,H)$ = 15.2 Hz, 2H, CH_2Ph), 3.73 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 165.3 (*C*=O), 160.5 (CO_2Me), 133.7 (1 C_{Ar}), 129.0, 128.4, 128.3 (5 CH_{Ar}), 123.6 (q, $^1J(C,F)$ = 280.0 Hz, CF_3), 55.6 (*C*(3)H), 53.2 (OCH_3), 52.9 (q, $^2J_{C,F}$ = 35.1 Hz, *C*(4)H), 46.1 (CH_2Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –73.94 (d, $^3J(H,F)$ = 6.1 Hz, 3F, CF_3); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{13}H_{12}F_3NO_3Na$, 310.0662, found 310.0660.

***trans*-*N*-Benzyl-3-(*tert*-butyl)-2-(trifluoromethyl)azetidin-2-one (*trans*-4e).** Colorless oily *β*-lactam ***trans*-4e** (129 mg, 45% yield, purification on SiO_2, using petroleum ether/AcOEt = 95:5, less polar fraction); IR (film): ν_{max}/cm^{-1} 3037w, 2963s, 2875w, 1770vs (C=O), 1471w, 1383s, 1283s, 1171vs, 1130vs, 696s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.39–7.34 (m, 3 CH_{Ar}), 7.30–7.29 (m, 2 CH_{Ar}), 4.93, 3.90 (AB system, 2d, $^2J(H,H)$ = 15.0 Hz, 2H, CH_2Ph), 3.54 (dq, $^3J(H,H)$ = 2.4 Hz, $^3J(H,F)$ = 6.0 Hz, 1H, C(4)*H*), 3.10 (d, $^3J(H,H)$ = 2.4 Hz, 1H, C(3)*H*), 0.99 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 167.5 (*C*=O), 134.8 (1 C_{Ar}), 128.8, 128.7, 128.1 (5 CH_{Ar}), 124.7 (q, $^1J(C,F)$ = 278.0 Hz, CF_3), 62.7 (*C*(3)H), 52.5 (q, $^2J(C,F)$ = 33.6 Hz, *C*(4)H), 45.2 (CH_2Ph), 31.0 (*C*(CH_3)$_3$), 27.0 (C(CH_3)$_3$); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –73.13 (d, $^3J(H,F)$ = 5.7 Hz, 3F, CF_3); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{15}H_{18}F_3NONa$, 308.1238, found 308.1237.

***cis*-*N*-Benzyl-3-(*tert*-butyl)-2-(trifluoromethyl)azetidin-2-one (*cis*-4e).**

Colorless oily *β*-lactam ***cis*-4e** (40 mg, 14% yield, purification on SiO_2, using petroleum ether/AcOEt = 90:10, more polar fraction); IR (film): ν_{max}/cm^{-1} 3033w, 2961s, 2918s, 2872s, 1765vs (C=O), 1397s, 1281s, 1171vs, 1157vs, 1125vs, 694s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.39–7.32 (m, 3 C*H*$_{Ar}$), 7.27–7.26 (m, 2 C*H*$_{Ar}$), 4.91, 3.96 (AB system, 2d, $^2J_{H,H}$ = 15.0 Hz, 2H, C*H*$_2$Ph), 3.84, 3.83 (2dq, $^3J(H,H)$ = 7.9 Hz, $^3J(H,F)$ = 18.0 Hz, 1H, C(4)*H*), 3.34 (d, $^3J(H,H)$ = 7.9 Hz, 1H, C(3)*H*), 1.16 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 168.5 (*C*=O), 134.9 (1 *C*$_{Ar}$), 128.9, 128.5, 128.0 (5 *C*H$_{Ar}$), 124.8 (q, $^1J(C,F)$ = 277.8 Hz, *C*F$_3$), 65.4 (*C*(3)H), 52.2 (q, $^2J(C,F)$ = 34.8 Hz, *C*(4)H), 45.2 (*C*H$_2$Ph), 31.5 (*C*(CH$_3$)$_3$), 28.4 (q, $J(C,F)$ = 2.2 Hz, C(*C*H$_3$)$_3$); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –65.38 (d, $^3J(H,F)$ = 7.9 Hz, 3F, C*F*$_3$); HRMS/ESI *(m/z)* [M+Na]$^+$ calcd for $C_{15}H_{18}F_3NONa$, 308.1238, found 308.1235.

***trans*-*N*-Benzyl-3-ferrocenyl-2-(trifluoromethyl)azetidin-2-one (*trans*-4f)**.

Orange solid *β*-lactam ***trans*-4f** (290 mg, 70% yield), purification on SiO_2, using petroleum ether/AcOEt = 90:10); m.p. 101–103 ºC; IR (KBr): ν_{max}/cm^{-1} 3084w, 3028w, 2922w, 1747vs (C=O), 1405m, 1297m, 1191s, 1148s, 1127s, 694w; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.42–7.39 (m, 2 C*H*$_{Ar}$), 7.37–7.34 (m, 3 C*H*$_{Ar}$), 4.92, 4.08 (AB system, 2d, $^2J(H,H)$ = 15.0 Hz, 2H, C*H*$_2$Ph), 4.21-4.19 (m, 1H, C(3)*H*), 4.18 (brs, 7H, Fc), 4.11, 4.07 (2 brs, 2H, Fc), 3.73 (dq, $^3J(H,H)$ = 2.9 Hz, $^3J(H,F)$ = 7.2 Hz, 1H, C(4)*H*); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 166.1 (*C*=O), 134.8 (1 *C*$_{Ar}$), 129.0, 128.6, 128.3 (5 *C*H$_{Ar}$), 124.4 (q, $^1J(C,F)$ = 278.3 Hz, *C*F$_3$), 69.0 (5 *C*H(Fc)), 79.7 (*C*(Fc)), 68.5, 68.4, 67.1, 66.7 (4 *C*H(Fc)), 58.2 (q, $^2J(C,F)$ = 36.2 Hz, *C*(4)H), 52.3 (brq, $^3J(C,F)$ = 1.3 Hz, *C*(3)H), 45.6 (*C*H$_2$Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –73.49 (d, $^3J(H,F)$ = 5.9Hz, 3F, C*F*$_3$); HRMS/ESI *(m/z)* [M+Na]$^+$ calcd for $C_{21}H_{18}F_3NONaFe$, 436.0588, found 436.0586.

***trans*-*N*-Benzyl-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)azetidin-2-one ((*R*)-*trans*-4g).**

Pale yellow solid *β*-lactam **(*R*)-*trans*-4g** (156 mg, 48% yield, purification on SiO_2, using petroleum ether/AcOEt = 96:4, less polar fraction); m.p. 49–51 ºC; $[\alpha]_D^{22}$ = –55.6 (c 1.0 in DCM); IR (KBr): ν_{max}/cm^{-1} 2994w, 2929w, 1754vs (C=O), 1455w, 1383s, 1293s, 1166vs, 1125vs, 1071s, 832w, 697s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.39–7.33 (m, 5 C*H*$_{Ar}$), 4.95, 3.99 (AB system, 2d, $^2J_{H,H}$ = 12.0 Hz, 2H, C*H*$_2$Ph), 4.35 (dt, $^3J(H,H)$ = 3.0 Hz, $^4J(H,H)$ = 1.0 Hz, 1H, C*H*OC(CH$_3$)$_2$), 4.11–4.06 (m, 2H,

C*H*$_2$OC(CH$_3$)$_2$), 3.93 (dq, ^{3}*J(H,H)* = 1.8 Hz, ^{3}*J(H,F)* = 6.0 Hz, 1H, C(4)*H*), 3.50–3.48 (m, 1H, C(3)*H*), 1.44, 1.37 (2s, 6H, 2 C*H*$_3$); ^{13}C NMR (150 MHz, CDCl$_3$), *δ*: 165.3 (*C*=O), 134.4 (1 *C*$_{Ar}$), 128.8, 128.5, 128.1 (5 *C*H$_{Ar}$), 124.4 (q, ^{2}*J(C,F)* = 277.5 Hz, *C*F$_3$), 110.1 ((CH$_3$)$_2$*C*O$_2$), 71.9 (*C*H$_2$OC(CH$_3$)$_2$)), 66.1 (*C*HOC(CH$_3$)$_2$), 53.3 (brd, *C*(3)H), 53.3 (brs, *C*H$_2$OC(CH$_3$)$_2$), 53.0 (q, ^{2}*J(C,F)* = 34.4 Hz, *C*(4)H), 45.6 (*C*H$_2$Ph), 25.7, 26.2 (2 *C*H$_3$); ^{19}F NMR (565 MHz, CDCl$_3$), *δ*: –68.80 (d, ^{3}*J(H,F)* = 7.2 Hz, 3F, C*F*$_3$); HRMS/ESI *(m/z)* [M+Na]$^+$ calcd for C$_{16}$H$_{18}$F$_3$NO$_3$Na, 352.1136, found 352.1134.

***cis*-*N*-Benzyl-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(trifluoromethyl)azetidin-2-one ((*R*)-*cis*-4g** and **(*R*)-*cis*-4g').**

Pale yellow semi-solid *β*-lactams **(*R*)-*cis*-4g** and **(*R*)-*cis*-4g'** (85:15 mixture of diastereoisomers; 111 mg, 34% yield, purification on SiO$_2$, using petroleum ether/AcOEt = 92:8, more polar fraction); m.p. 48–49 ºC; [*α*]$_D^{22}$ = –69.5 (c 1.0 in DCM); IR (KBr): ν_{max}/cm^{-1} 2987s, 2936w, 2890w, 1774vs (C=O), 1460s, 1367s, 1286vs, 1191vs, 1139vs, 1055vs, 848s, 711s, 692s; ^{1}H NMR (600 MHz, CDCl$_3$), *δ*: Major diastereoisomer: 4.90, 4.02 (AB system, 2d, ^{2}*J(H,H)* = 12.0 Hz, 2H, C*H*$_2$Ph), 3.93 (dq, ^{3}*J(H,F)* = 6.0 Hz, ^{3}*J(H,H)* = 2.2 Hz, 1H, C(4)*H*), Minor diastereoisomer : 4.94 (d, ^{2}*J(H,H)* = 12.0 Hz, 1H of AB system from C*H*$_2$Ph), 3.90–3.86 (m, 1H, C(4)*H*), Both diastereoisomers: 7.40–7.31 (m, 5 C*H*$_{Ar}$), 3.80–3.70 (m, 4H, 1H of AB system from C*H*$_2$Ph (minor isomer), 2H, C*H*$_2$OC(CH$_3$)$_2$), 1H, C*H*OC(CH$_3$)$_2$), 1.29, 1.19 (2s, 6H, 2 C*H*$_3$); ^{13}C NMR (150 MHz, CDCl$_3$), *δ*: Major diastereoisomer: 165.2 (*C*=O), 134.6 (1 *C*$_{Ar}$) 129.0, 128.4, 128.2 (5 *C*H$_{Ar}$), 124.4 (q, ^{2}*J(C,F)* = 278.6 Hz, *C*F$_3$), 110.1 (CH$_3$)$_2$*C*O$_2$), 71.9 (*C*H$_2$OC(CH$_3$)$_2$), 66.1 (*C*HOC(CH$_3$)$_2$), 56.4 (*C*(3)H), 52.9 (q, ^{2}*J(C,F)* = 33.8 Hz, *C*(4)H), 45.6 (*C*H$_2$Ph), 14.8, 15.2 (2 *C*H$_3$), Minor diastereoisomer: 167.1 (*C*=O), 134.0 (1 *C*$_{Ar}$), 128.9, 128.4, 128.2 (5 *C*H$_{Ar}$), 124.3 (q, ^{2}*J(C,F)* = 278.0 Hz, *C*F$_3$), 67.2 (*C*H$_2$OC(CH$_3$)$_2$)), 64.0 (*C*HOC(CH$_3$)$_2$), 56.4 (*C*(3)H), 52.2 (q, ^{2}*J(C,F)* = 34.7 Hz, *C*(4)H), 46.0 (*C*H$_2$Ph), (CH$_3$)$_2$*C* and (*C*H$_3$)$_2$C) not found; ^{19}F NMR (565 MHz, CDCl$_3$), *δ*: Major diastereoisomer: –68.80 (d, ^{3}*J(H,F)* = 6.2 Hz, 3F, C*F*$_3$), Minor diastereoisomer: –73.78 (d, ^{3}*J(H,F)* = 6.0 Hz, 3F, C*F*$_3$); HRMS/ESI *(m/z)* [M+Na]$^+$ calcd for C$_{16}$H$_{18}$F$_3$NO$_3$Na, 352.1136, found 352.1136.

***trans*-*N*-(*S*)-Methylbenzyl-3-phenyl-2-(trifluoromethyl)azetidin-2-one ((*S*)-*trans*-4h).**

Colorless semi-solid *β*-lactam **(*S*)-*trans*-4h** (51 mg, 16% yield, purification on SiO_2, using petroleum ether/AcOEt = 97:3, least polar fraction); m.p. 70–71 ºC; $[\alpha]_D^{22}$ = –23.2 (c 1.0 in DCM); IR (KBr): ν_{max}/cm^{-1} 3026w, 2980w, 2933w, 1747vs (C=O), 1493w, 1358w, 1276s, 1195s, 1172s, 700s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.41–7.32 (m, 8 C*H*$_{Ar}$), 7.24–7.23 (m, 2 C*H*$_{Ar}$), 4.61 (q, $^3J(H,H)$ = 7.2 Hz, 1H, CH_3CH(Ph)), 4.39 (brs, 1H, C(3)*H*), 3.80 (dq, $^3J(H,H)$ = 2.4 Hz, $^3J(H,F)$ = 6.1 Hz, 1H, C(4)*H*), 1.91 (d, $^3J(H,H)$ = 7.2 Hz, 3H, CH_3CH(Ph)); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 166.5 (*C*=O), 140.7, 132.9 (2 *C*$_{Ar}$), 129.1, 128.9, 128.2, 128.1, 127.3, 126.7 (10 *C*H$_{Ar}$), 124.3 (q, $^1J(C,F)$ = 278.3 Hz, *C*F_3), 57.7 (q, $^2J(C,F)$ = 33.6 Hz, *C*(4)H), 56.1 (CH_3*C*H(Ph)), 55.5 (*C*(3)H), 19.8 (*C*H_3CH(Ph)); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –73.97 (d, $^3J(H,F)$ = 6.1 Hz, 3F, CF_3); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{18}H_{16}F_3NONa$, 342.1073, found 342.1072.

***trans*-*N*-(*S*)-Methylbenzyl-3-phenyl-2-(trifluoromethyl)azetidine-2-one ((*S*)-*trans*-4h').**

Colorless semi-solid *β*-lactam **(*S*)-*trans*-4h'** (122 mg, 38% yield, purification on SiO_2, using petroleum ether/AcOEt = 95:5, medium polar fraction); m.p. 71–72 ºC; $[\alpha]_D^{22}$ = –30.8 (c 1.0 in DCM); IR (KBr): ν_{max}/cm^{-1} 3032w, 2983w, 2931w, 1747vs (C=O), 1457s, 1345s, 1285s, 1198s, 1168s, 1130vs, 700vs; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.42–7.41 (m, 4 C*H*$_{Ar}$), 7.37–7.31 (m, 4 C*H*$_{Ar}$), 7.20–7.19 (m, 2 C*H*$_{Ar}$), 5.21 (q, $^3J(H,H)$ = 7.0 Hz, 1H, CH_3CH(Ph)), 4.38 (d, $^3J(H,H)$ = 2.4 Hz, 1H, C(3)*H*), 3.72 (dq, $^3J(H,H)$ = 2.4 Hz, $^3J(H,F)$ = 6.0 Hz, 1H, C(4)*H*), 1.71 (d, $^3J(H,H)$ = 7.0 Hz, 3H, CH_3CH(Ph)); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 166.6 (*C*=O), 138.6, 132.8 (2 *C*$_{Ar}$), 129.1, 128.9, 128.2, 128.1, 127.3, 127.2 (10 *C*H$_{Ar}$), 124.3 (q, $^1J(C,F)$ = 277.7 Hz, *C*F_3), 58.1 (q, $^2J(C,F)$ = 34.2 Hz, *C*(4)H), 55.8 (*C*(3)H), 52.2 (CH_3*C*H(Ph)), 17.9 (*C*H_3CH(Ph)); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –73.70 (d, $^3J(H,F)$ = 6.2 Hz, 3F, CF_3); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{18}H_{16}F_3NONa$, 342.1073, found 342.1074.

***cis*-*N*-(*S*)-Methylbenzyl-3-phenyl-2-(trifluoromethyl)azetidin-2-one ((*S*)-*cis*-4h).**

Colorless solid *β*-lactam **(*S*)-*cis*-4h** (21 mg, 7% yield, purification on SiO_2, using petroleum ether/AcOEt = 92:8, most polar fraction); m.p. 71–73 ºC; $[\alpha]_D$ = –26.9 (c 1.0 in DCM); IR (KBr): ν_{max}/cm^{-1} 3066w, 3030w, 2928w, 1750vs (C=O), 1450m, 1360m, 1290s, 1186s, 1141vs, 1105s, 710s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: 7.34–7.30 (m, 5 C*H*$_{Ar}$), 7.27–7.22 (m, 3 C*H*$_{Ar}$), 7.21–7.18 (m, 2 C*H*$_{Ar}$), 5.15 (q, $^3J(H,H)$ =

7.2 Hz, 1H, CH_3CH(Ph)), 4.55 (d, $^3J(H,H)$ = 6.0 Hz, 1H, C(3)*H*), 3.90–3.86 (m, 1H, C(4)*H*), 1.60 (d, $^3J(H,H)$ = 7.2 Hz, 3H, CH_3CH(Ph)); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 167.0 (*C*=O), 138.4, 130.3 (2 C_{Ar}), 129.4, 128.9, 128.5, 128.3, 128.2, 127.3 (10 CH_{Ar}), 123.6 (q, $^1J(C,F)$ = 278.3 Hz, CF_3), 56.6 (*C*(3)H), 55.8 (q, $^2J(C,F)$ = 33.0 Hz, *C*(4)H), 52.0 (CH_3CH(Ph)), 18.0 (CH_3CH(Ph)); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –68.47 (d, $^3J(H,F)$ = 6.8 Hz, 3F, CF_3); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{18}H_{16}F_3NONa$, 342.1078, found 342.1073.

***trans/cis-N*-Benzyl-2-difluoromethyl-3-phenylazetidin-2-one (*trans/cis*-4i).**

Colorless oily *β*-lactams **t*rans/cis*-4i** (70:30 mixture of diastereoisomers; 267 mg, 93% yield, purification on SiO_2, using petroleum ether/AcOEt = 94:6); IR (film): ν_{max}/cm^{-1} 3087w, 3064w, 3026s, 2937w, 1767vs (C=O), 1602w, 1493s, 1446s, 1387s, 1075s, 691s; ^{1}H NMR (600 MHz, $CDCl_3$), *δ*: Major diastereoisomer: 5.40 (ddd, $^2J(H,F(1))$ = 60.1 Hz, $^2J(H,F(2))$ = 56.1 Hz, $^3J(H,H)$ = 6.4 Hz, 1H, CHF_2), 4.93, 4.17 (AB system, 2d, $^2J(H,H)$ = 14.8 Hz, 2H, CH_2Ph), 4.65 (d, $^3J(H,H)$ = 5.8 Hz, 1H, C(3)*H*), 3.91–3.87 (m, 1H, C(4)*H*); Minor diastereoisomer: 5.91 (td, $^2J(H,F)$ = 55.0 Hz, $^3J(H,H)$ = 4.2 Hz, 1H, CHF_2), 4.85, 4.24 (AB system, 2d, $^2J(H,H)$ = 15.0 Hz, 2H, CH_2Ph), 4.36 (d, $^3J(H,H)$ = 2.0 Hz, 1H, C(3)*H*), 3.74–3.70 (m, 1H, C(4)*H*); Both diastereoisomers: 7.43–7.29 (m, 18 CH_{Ar}), 7.26–7.25 (m, 2 CH_{Ar}); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 166.9 (*C*=O), 167.0 (*C*=O), 135.3, 135.2, 133.4, 130.8 (4 C_{Ar}), 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0 (20 CH_{Ar}), 115.5 (t, $^2J(C,F)$ = 21.1 Hz, CHF_2), 115.0 (t, $^2J(C,F)$ = 21.1 Hz, CHF_2), 55.6 (t-like, $^2J(C,F)$ = 12.0 Hz, *C*(4)H), 55.4 (dd, $^2J(C,F(1))$ = 30.0 Hz, $^2J(C,F(2))$ = 20.1 Hz, *C*(4)H), 46.0, 45.9 (2brs, 2 CH_2Ph); ^{19}F NMR (565 MHz, $CDCl_3$), *δ*: –123.62, –123.71 (2t, *J* = 7.7 Hz, CHF_2 (Major diastereoisomer)), –120.20, –123.54 (2ddd, $^2J(F,F)$ = 304.5 Hz, $^2J(H,F)$ = 53.8 Hz, $^3J(H,F)$ = 6.4 Hz, CHF_2 (Minor diastereoisomer)); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{17}H_{15}F_2NONa$, 310.1011, found 310.1019.

***trans/cis-N*-(*S*)-methylbenzyl-2-(Difluoromethyl)-3-phenylazetidin-2-one (*trans/cis*-4j).**

Colorless solid *β*-lactams **t*rans/cis*-4j** (73:18:9 inseparable mixture of diastereoisomers A, B, and C; 169 mg, 58% yield, purification on SiO_2, using petroleum ether/AcOEt = 92:8); m.p. 73–76 ºC; $[\alpha]_D$ = –26.9 (c 1.0 in DCM). IR (KBr): ν_{max}/cm^{-1} 3065w, 3035w, 2988w, 2938w, 1738vs (C=O), 1495s, 145s, 1349s, 1161s,

1131vs, 1054vs, 756s, 695vs; ^{1}H NMR (600MHz, $CDCl_3$), *δ*: Diastereoisomer A (73%): 5.83 (dt, $^{2}J(H,F)$ = 55.0 Hz, $^{3}J(H,H)$ = 3.8 Hz, 1H, C*H*F_2), 5.12 (q, $^{3}J(H,H)$ = 7.2 Hz, 1H, CH_3C*H*(Ph)), 4.30 (d, $^{3}J(H,H)$ = 2.3 Hz, 1H, C(3)*H*), 3.63–3.59 (m, 1H, C(4)*H*), 1.73 (d, 3H, $^{3}J(H,H)$ = 7.2 Hz, C*H*$_3$CH(Ph)); Diastereoisomer B (18%): 5.66 (dt, $^{2}J(H,F)$ = 55.2 Hz, $^{3}J(H,H)$ = 3.8 Hz, 1H, C*H*F_2), 4.83 (q, $^{3}J(H,H)$ = 7.2 Hz, 1H, CH_3C*H*(Ph)), 4.31 (d, $^{3}J(H,H)$ = 2.4 Hz, 1H, C(3)*H*), 3.73–3.69 (m, 1H, C(4)*H*), 1.85 (d, 3H, $^{3}J(H,H)$ = 7.2 Hz, C*H*$_3$CH(Ph)); Diastereoisomer C (9%): 5.62–5.57 (m, 1H, C*H*F_2), 4.70 (q, $^{3}J(H,H)$ = 7.2 Hz, 1H, CH_3C*H*(Ph)), 4.58 (t-like, $^{3}J(H,H)$ and $^{4}J(H,H)$ = 5.6 Hz, 1H, C(3)*H*), 3.90–3.80 (m, 1H, C(4)*H*), 1.92 (d, 3H, $^{3}J(H,H)$ = 7.3 Hz, C*H*$_3$CHPh); All three diastereoisomers: 7.22–7.20 (m, 6 C*H*$_{Ar}$), 7.44–7.27 (m, 24 C*H*$_{Ar}$); ^{13}C NMR (150 MHz, $CDCl_3$), *δ*: 167.1, 167.0, 166.9 (3 *C*=O), 139.4, 133.6 (*C*$_{Ar}$), 129.0, 128.9, 128.2, 127.9, 127.4, 127.2, 126.9, 126.8 (30 *C*H$_{Ar}$), 115.0, 114.6, 114.5 (3 t, $^{2}J(C,F)$ = 241.5 Hz, *C*HF_2), 59.3, 58.6, 54.7 (3t-like, $^{3}J(H,H)$ = 26.3 Hz, *C*(4)H), 54.3, 52.7, 52.5 (CH_3*C*H(Ph)), 19.3, 19.1, 18.8 ppm (3 *C*H_3); ^{19}F {^{1}H} NMR (188 MHz, $CDCl_3$), *δ*: –125.0, –123.2 (AB system, $^{2}J(F,F)$ = 292.8 Hz (Diastereoisomer A)), –125.2, –123.5 (AB system, $^{2}J(F,F)$ = 294.2 Hz (Diastereoisomer B)), –122.8, –120.7 (AB system, $^{2}J(F,F)$ = 302.6 Hz (Diastereoisomer C)); HRMS/ESI *(m/z)* $[M+Na]^+$ calcd for $C_{18}H_{17}F_2NONa$, 302.1353, found 302.1351.

X-Ray Crystal Structure Determination of 4a. All measurements were made on an *Agilent Technologies SuperNova* area-detector diffractometer[20] using Cu*Kα* radiation (*λ* = 1.54184 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler. The data collection and refinement parameters are given below[21] and a view of the molecule is shown in Fig. 2. Data reduction was performed with *CrysAlisPro*.[20] The intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction using spherical harmonics[20] was applied. Equivalent reflections, other than Friedel pairs, were merged. The structure was solved by direct methods using *SHELXS-2014*,[22] which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the *H*-atoms were placed in geometrically calculated positions and refined by using a riding model where each *H*-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent *C*-atom. The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which

minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied. The structure was refined as an inversion twin, but the precision of the absolute structure parameter,[23] 0.44(16), is too low for this parameter to be a sufficient indicator of the true absolute structure. Neutral atom scattering factors for non-H-atoms were taken from ref.[24], and the scattering factors for *H*-atoms were taken from ref.[25] Anomalous dispersion effects were included in F_c;[26] the values for *f′* and *f″* were those of ref.[27] The values of the mass attenuation coefficients are those of ref.[28] All calculations were performed using the *SHELXL*-2014[29] program.

Crystal data for **4a**: $C_{17}H_{14}F_3NO$, M = 305.29, crystallized from diisopropyl ether/*n*-heptane, colorless, prism, crystal dimensions 0.15 × 0.16 × 0.30 mm, monoclinic, space group $P2_1$, Z = 2, reflections for cell determination 5244, 2θ range for cell determination 7 – 152°, a = 11.9664(4) Å, b = 5.54706(14) Å, c = 12.4674(5) Å, β = 115.633(4), V = 746.12(5) Å^3, T = 160(1) K, D_X = 1.359 g·cm^{-3}, μ(Cu$K\alpha$) = 0.940 mm^{-1}, scan type ω, $2\theta_{(max)}$ = 153.1°, transmission factors (min; max) = 0.519; 1.000, total reflections measured 8153, symmetry independent reflections 2954, reflections with $I > 2\sigma(I)$ 2817, reflections used in refinement 2954, parameters refined 200, restraints 1, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0301, $wR(F^2)$ [all data] = 0.0822 ($w = [\sigma^2(F_o^2) + (0.0456P)^2 + 0.0903P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$), goodness of fit 1.034, final Δ_{max}/σ 0.000, $\Delta\rho$ (max; min) = 0.12; –0.14 e Å^{-3}.

Acknowledgements

This work is a part of the planned Ph.D. thesis of M. K. Kowalski, University of Łódź. Authors acknowledge the National Science Center (PL-Cracow) for financial support (**Grant OPUS–7** (UMO–2014/13/B/ST5/04004)).

Supplementary data

Supplementary data related to this article can be found at ……..

References and notes

1. (*a*) I. G. Gunda, Ed., *The Organic Chemistry of β-Lactams*, VCH, New York, NY, 1993; (*b*) K. Lewis, *Nat. Rev. Drug Discov.* **2013**, *12*, 371–387; (*c*) P. A.

Mariotis, *Eur. J. Org. Chem.* **2014**, 2647–2657; (*d*) C. R. Pitts, T. Lectka, *Chem. Rev.* **2014**, *114*, 7930–7953.

2. (*a*) J. Wang, M. Sanchez-Rosello, J. L. Aceňa, C. del Pozo, A. E. Sorochinsky, S. V. Fustero, A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; (*b*) V. Nenajdenko, Ed., *Fluorine in Heterocyclic Chemistry*, **Vol. 1 and 2**, Springer Verlag, Berlin, 2013; (*c*) V. A. Petrov, Ed., *Fluorinated Heterocyclic Compounds*, J. Wiley & Sons, Inc., Hoboken, NJ, 2009.
3. G. O. Danelon, O. A. Mascaretti, *J. Fluorine Chem.* **1992**, *56*, 109–140.
4. (*a*) I. Ojima, J. C. Slater, P. Pera, J. M. Veith, A. Abouabdellah, J.-P. Bégué, R. J. Bernacki, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 133–138; (*b*) A. Abouabdellah, J.-P. Bégué, D. Bonnet-Delpon, T. T. T. Nga, *J. Org. Chem.* **1997**, *62*, 8826–8833; (*c*) L. Kuznetsova, I. M. Ungureanu, A. Pepe, I. Zanardi, X. Wu, I. Ojima, *J. Fluorine Chem.* **2004**, *125*, 487–500; (*d*) L. V. Kuznetsova, A. Pepe, I. M. Ungureanu, P. Pera, R. J. Bernacki, I. Ojima, *J. Fluorine Chem.* **2008**, *129*, 817–828.
5. (a) G. Guanti, L. Banfi, E. Narisano, C. Scolastico, E. Bosone, *Synthesis* 1985, 609–611; (b) T. Kagawa, K. Fujita, K. Kawada, *J. Fluorine Chem.* **2013**, *152*, 77–80.
6. Y. Gong, K. Kato, *J. Fluorine Chem.* **2001**, *111*, 77–80.
7. (a) P. F. Bevilacqua, D. D. Keith, J. L. Roberts, *J. Org. Chem.* **1984**, *49*, 1430–1434; (b) P. Davoli, A. Forni, C. Franciosi, I. Moretti, F. Prati, *Tetrahedron: Asymmetry* **1999**, *10*, 2361–2371; (c) Y. Liu, J.-L. Chen, G.-H. Wang, P. Sun, H. Huang, F.-L. Qing, *Tetrahedron Lett.* **2013**, *54*, 5541–5543.
8. V. Petrik, G.-V. Röschenthaler, D. Cahard, *Tetrahedron* **2011**, *67*, 3254–3259.
9. S. Decamps, L. Sevaille, S. Ongeri, B. Crousse, *Org. Biomol. Chem.* **2014**, *12*, 6345–6348.
10. M. Kinugasa, S. Hashimoto, *J. Chem. Soc., Chem. Commun.* **1972**, 466–467.
11. (a) J. Marco-Coutelles, *Angew. Chem. Int. Ed.* **2004**, *43*, 2198–2200; (b) R. Pal, S. C. Ghosh, K. Chandra, A. Basak, *Synlett* 2007, 2321–2330; (c) B. Mandal, B. Basu, *Top. Heterocycl. Chem.* **2013**, *30*, 85–110; (d) R. K. Khangarot, K. P. Kaliappan, *Eur. J. Org. Chem.* **2013**, 7664–7677; (e) S. Stecko, B. Furman, M. Chmielewski, *Tetrahedron* 2014, **70**, 7817–7844; (f) M. Chigrinova, D. A. Mackenzie, A. R. Sherratt, L. L. W. Cheung, J. P. Pezacki, *Molecules* **2015**, *20*, 6959–6969; (g) L. Mucha, P. Kamil, O. Staszewska-Krajewska, S. Stecko, A.

Ulikowski, J. Frelek, A. Suszyńska, M. Chmielewski, B. Furman, *Tetrahedron: Asymmetry* **2016**, *27*, 12–21.

12. (a) Z. Chen, L. Liu, M. Wang, X. Liu, X. Feng, *Chem. Eur. J.* **2013**, *19*, 7651–7567; (b) S. Santaro, R.-Z. Liao, T. Marcelli, P. Hammar, F. Himo, *J. Org. Chem.* **2015**, *80*, 2649–2660.
13. A. N. El Dine, D. Grée, T. Roisnel, E. Caytan, A. Hachem, R. Grée, *Eur. J. Org. Chem.* **2016**, 556–561.
14. (a) G. Mlostoń, E. Obijalska, M. Celeda, V. Mittermeier, A. Linden, H. Heimgartner, *J. Fluorine Chem.* 2014, **165**, 27–32; (b) K. Tanaka, M. Ohsuga, Y. Sugimoto, Y. Okafuji, K. Mitsuhashi, *J. Fluorine Chem.* **1988**, *39*, 39–45; (c) K. Tanaka, Y. Sugimoto, Y. Okafuji, M. Tachikawa, K. Mitsuhashi, *J. Heterocyclic Chem.* **1989**, *26*, 381–385; (d) T. Milcent, N. Hinks, D. Bonnet-Delpon, B. Crousse, *Org. Biomol. Chem.* **2010**, *8*, 3025–3030.
15. H. Tanaka, A. K. M. Abdul Hai, M. Sadakane, H. Okumoto, S. Tarii, *J. Org. Chem.* **1994**, *59*, 3040–3046.
16. C.K. Johnson, *ORTEPII*, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
17. (a) J.-H. Chen, S.-H. Liao, X.-L. Sun, Q. Shen, Y. Tang, *Tetrahedron* **2012**, *68*, 5042–5045; (b) M.-C. Ye, J. Zhou, Y. Tang, *J. Org. Chem*. **2006**, *71*, 3576–3582.
18. a) W. Van Brabandt, N. De Kimpe, *Synlett* **2006**, 2039–2042; b) H. D. Thi, L. Decuyper, K. Mollet, S. Kenis, N. De Kimpe, T. Van Nguyen, M. D'hooghe, *Synlett* **2016**, *27*, 1100–1105.
19. (a) S. G. Davies, Ch. J. Goodwin, D. Hepworth, P. M. Roberts, J. E. Thomson, *J. Org*. *Chem*. **2009**, *75,* 1214-1227; (b) D. A. Tickell, M. F. Mahon, S. D. Bull, T. D. James, *Org*. *Lett*. **2013**, *15*, 860–863.
20. *CrysAlisPro*, Version 1.171.37.35g, Agilent Technologies, Yarnton, Oxfordshire, England, 2014.
21. CCDC-1454792 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* www.ccdc.cam.ac.uk/getstructures.
22. G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112–122.
23. (a) H. D. Flack, G. Bernardinelli, *Acta Crystallogr. Sect. A* **1999**, *55*, 908–915; (b) H. D. Flack, G. Bernardinelli, *J. Appl. Crystallogr.* **2000**, *33*, 1143–1148; (c)

S. Parsons, H. D. Flack, T. Wagner, *Acta Crystallogr. Sect. B* **2013**, *69*, 249–259.

24. E. N. Maslen, A. G. Fox, M. A. O'Keefe, in *'International Tables for Crystallography'*, Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, **1992**, *Vol. C*, Table 6.1.1.1, pp. 477–486.
25. D. C. Creagh, W. J. McAuley, in *'International Tables for Crystallography'*, Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, **1992**, *Vol. C*, Table 4.2.6.8, pp. 219–222.
26. D. C. Creagh, J. H. Hubbell, in *'International Tables for Crystallography'*, Ed. A. J. C. Wilson, Kluwer Academic Publishers, Dordrecht, **1992**, *Vol. C*, Table 4.2.4.3, pp. 200–206.
27. R. F. Stewart, E. R. Davidson, W. T. Simpson, *J. Chem. Phys.* **1965**, *42*, 3175–3187.
28. J. A. Ibers, W. C. Hamilton, *Acta Crystallogr.* **1964**, *17*, 781–782.
29. G. M. Sheldrick, *Acta Crystallogr. Sect. C* **2015**, *71*, 3–8.